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Abstract: The COVID-19 pandemic has created major insecurities regarding whether we can and should maintain the current standards of diagnosis and treatment and access to care for patients with cancer. This is particularly true in the field of neuro-oncology, where the perceived benefit of therapeutic interventions is often low, although this notion is partially incorrect. We acknowledge that the recommendations for care of patients with cancer have become a moving target and that all recommendations are subject to modification based on national and institutional regulations. Still, some important considerations and proposals may apply broadly. First, it is important to note that old age and cardiovascular and pulmonary co-morbidities are the major risk factors for experiencing a severe course of and for dying of COVID-19, not chronic immunosuppression and cancer. Second, many of the considerations on how we should adapt clinical practice in neuro-oncology in view of COVID-19 that are now dominating discussions at local tumour boards, as well as on the institutional level and within societies of neuro-oncology, are not novel but have been valid before and only now have become a priority. More than ever, it seems to be mandatory to adhere to evidence-based medicine and not to prescribe potentially toxic, notably immunsuppresssive systemic therapy where evidence for efficacy is low. Furthermore, it is more obvious now that oncologists must not miss the right time for advance care planning, that is, supporting patients in understanding and sharing their personal values, life goals and preferences regarding future medical care. The major psychological impact of transforming oncology care to teleconferences and videoconferences and of the important strict recommendation of social distancing must not be overlooked in a patient population that is characterised by significant prevalence of cognitive decline and by the general perception that their life span may not exceed the life span of the COVID-19 pandemic.

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How we treat brain tumor patients during the COVID-19 pandemic

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Coronavirus disease: COVID

O^6-methylguanine DNA methyltransferase: MGMT

Abstract

The COVID-19 pandemic has created major insecurities regarding whether we can and whether we should maintain the current standards of diagnosis and treatment and access to care for patients with cancer. This is particularly true in the field of Neuro-oncology where the perceived benefit of therapeutic interventions is often low, although this notion is partially incorrect. We acknowledge that recommendations for care of cancer patients have become a moving target and that all recommendations are subject to modification based on national and institutional regulations. Still, some important considerations and proposals may apply broadly. First, it is important to note that old age and cardiovascular and pulmonary comorbidities are the major risk factors for experiencing a severe course of and for dying of COVID-19, not chronic immunosuppression and not cancer. Second, many of the considerations on how we should adapt clinical practice in Neuro-Oncology in view of COVID-19that are now dominating discussions at local tumor boards as well as on institutional level and within societies of Neuro-oncology, are not novel, but have been valid before and only now become a priority. More than ever, it seems to be mandatory to adhere to evidence-based medicine, and not to prescribe potentially toxic, notably immunsuppresssive systemic therapy where evidence for efficacy is low. Furthermore, it is more obvious now that oncologists must not miss the right time for advance care planning, i.e. supporting patients in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The major psychological impact of transforming oncology care to teleconferences and videoconferences and of the important strict recommendation of social distancing must not be overlooked in a patient population that is characterized by significant prevalence of cognitive decline and by the general perception that their lifespan may

not exceed the lifespan of the COVID-19 pandemic.

Background

The coronavirus disease (COVID)-19 epidemic has changed the way medicine is practiced almost throughout the world. Age has emerged as the most impressive risk factor of succumbing to COVID-19. Among the large population of elderly patients who are treated for COVID-19, there is a strong prevalence of cardiovascular and pulmonary comorbidity, which suggests that frailty rather than age confers susceptibility to COVID-19. Thus the consideration that no resources should be invested into the elderly *per se*, e.g. by withholding admission to intensive care units for COVID-19 patients beyond a certain age, is therefore not only ethically questionable, but also scientifically false. Further, in contrast to what might be expected, chronic immunosuppression and cancer do not seem to be major predictors of COVID-19 vulnerability, although few data are available on this topic so far. Limited reports on COVID-19 and cancer which stem from China indicate that the disease course of COVID-19 may be more severe in cancer patients, but do not allow to definitely conclude that cancer as such increases the risk of COVID-19 (Zhang), however likely this may seem. Among 1524 cancer patients from a single institution in Wuhan, 12 patients (0.79%) has SARS-CoV-2 infection, which was higher than the cumulative incidence of 0.37% of COVID-19 cases in the respective general population (Yu). However, it is inappropriate to conclude that patients seen at a cancer center share the same risk factors of cardiopulmonary comorbidity and age as the general population. In a survey of 2007 COVID-19 cases from 575 hospitals in China, 18 patients had cancer (Liang), a figure that we do not interprete as evidence for strong associations between COVID-19 and cancer. The most common diagnosis was lung cancer (5 of 18 patients, 28%) and three quarter of the patients (12 of 18) were not undergoing active anti-cancer therapy, but were cancer survivors in routine follow-up. The authors stress that the rate of cancer among their COVID-19 patients

exceeds that of the general population, but without controlling for age and comorbidity, therefore, such figures need to be interpreted with caution. Accordingly, we need to make sure that we as health care providers stay informed and that we provide sufficient information to patients and caregivers on the relative risks and benefits of all interventions including anti-tumor treatments and supportive care. We need to outline that teleconferences and videoconsulting are valid alternatives, although hopefully a transient measure only. There is *a priori* no evidence to suggest that coming to an outpatient visit to hospital is more dangerous than going to visit relatives or for shopping. It is important to outline that it is not the hospital per se, but the number of other people encountered on the journey and the vigor with which social distancing is maintained that likely determines risk of infection. We must avoid inferior outcome of our patients simply because these are too afraid to come to hospital when in fact they should. Finally, we also need to make sure that we maintain the specialized Neuro-Oncology workforce at our institutions, e.g., by reorganizing multidisciplinary tumor boards to remote conferences or conferences with one decision maker per discipline only.

Considerations that are not new, but become more prominent during the COVID-19 pandemic

It is a common theme in Neuro-Oncology that therapeutic interventions for which there is no evidence should not routinely be offered to patients. It just seems to be so much easier for many health care providers and also caregivers to recommend specific medical interventions even in the absence of clear evidence, because it is perceived as easier and associated with less psychological burden than adequate advance care planning including an honest weighing of the options. Typical interventions that are often questionable include serial operations for tumors that

cannot be controlled surgically, repeat irradiation that is often combined with immunosuppressive steroids, or “salvage” chemotherapies beyond one or two alkylators for patients with gliomas, e.g., platinum-based regimens or irinotecan. These are just a few important measures commonly encountered in clinical practice for which no supportive data from controlled trials exist. It is only now that many of us realize that we occasionally treat where we should not. Further, we should prudently weigh risk and benefit of systemic pharmacotherapy in all disease areas where there is little or no evidence for pharmacotherapy at all, not only in meningioma or ependymoma in adults, but also in recurrent glioblastoma where no intervention except nitrosoureas in patients with tumors with O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation is likely to confer meaningful disease control. The attitude towards too generous corticosteroid prescriptions has already changed in recent years, but the time has come now to verify the need for steroid medication in every patient, notably also during radiotherapy where these agents are still occasionally given by default. On the other hand, treatments with clear benefits such as combined radiochemotherapy in MGMT promoter-methylated newly diagnosed glioblastoma should not be withheld from patients by default. This applies also to highly immunosuppressive treatments such as high-dose chemotherapy in primary central nervous system lymphoma.

Specific COVID-19 pandemic-related recommendations

There are also disease-specific considerations where the risk benefit ratio has changed. It is common practice to scan brain tumor patients in regular intervals even after years of stable disease without intervention. During the COVID-19 pandemic, we should explore whether we may delay repeat scanning and outpatient visits in patients in stable conditions who are asymptomatic. Radiotherapy schedules can

probably be adapted to hypofractionation in defined patient populations, e.g., patients with brain metastases or MGMT promoter-unmethylated glioblastoma, without compromising outcome, but with a major reduction in hospital visits. For systemic chemotherapy that is potentially immunosuppressive, including alkylating agent chemotherapy, dosing should be conservative and the tresholds for dose reductions may need to be lowered to improve safety, notably in diseases where prolonged exposure to treatment is probably needed, e.g., lower WHO grade gliomas.
Nobody would dispute that temozolomide would not have been approved based on the data observed in the patient population with glioblastoma lacking MGMT promoter methylation (Hegi). Yet, given the doubts on the reliability of assessing the MGMT status and the lack of alternative drugs approved in the newly diagnosed setting, temozolomide has been maintained as standard of care for all patients matching the inclusion criteria of the registration trial (Weller). One might argue that the cons currently overrule the pros when evaluating temozolomide for patients with MGMT promoter-unmethylated glioblastoma, given the risk of lymphopenia, repeated blood tests, and overall more contact with the health care system. Scepticism regarding alkylating agent chemotherapy is even more appropriate in the recurrent setting where neither temozolomide nor nitrosoureas offer major clinical benefit unless the MGMT promoter is methylated.

Access to intermediate and intensive care

The heated discussion on whether and which oncology patients, suffering from COVID-19 or not, should have access to intensive care medicine is an important one, but as yet in most countries mainly a preparation for a feared scenario where capacities are truly limited and triage becomes important. This cannot be regulated by recommendations in ESMO Open or elsewhere, but strongly depends on local

circumstances. What is important in the current situation is to indicate in any medical report somehow the overall prognosis of each patient to ascertain that those colleagues who have to make decisions under stress and time and resource limits are adequately informed. Patients with curatively operated tumors, e.g., schwannomas or meningiomas, who have no evidence of recurrent disease must not be placed in the same category as recurrent glioblastoma patients, but having a brain tumor is still often perceived as stigmatizing.

Clinical trials

Clinical trials deserve specific consideration in the situation of a pandemic as experienced now (De Paula). Phase I trials seeking to establish maximum tolerated doses with uncertain individual patient benefit need to be viewed with caution unless the intervention is highly unlikely to compromise immune function or to cause pulmonary toxicity. For most phase II trials, patients already enrolled onto trials and being stable may be kept on trial with a careful risk benefit ratio from the patient perspective, not from a trial perspective. Essentially the same holds true for phase III trials, however, clinical trials evaluating novel treatments that are associated with immunosuppression raise ethical concerns: randomizing in the current situation against a standard of care indicates that the benefit of the new intervention is uncertain, but the perceived risk of increased sensitivity to infection would seem to make it prohibitory to place patients on such trials. Particular concern applies to placebo-controlled trials in this situation. Resorting to teleconferences and videoconsultations and allowing drug shipment to patients include a few measures that may maintain trial integrity without placing patients at undue risk. Importantly, several companies sponsoring clinical trials have put activities on hold already, and, again, many institutions have imposed their own rules on how clinical research is

conducted and these regulations obviously overrule any outside recommendations.

Brain tumor patients with COVID-19 infection

Finally, as time goes by, brain tumor patients who have acquired COVID-19 infection will pose new challenges for Neuro-oncologists. For patients symptomatic for COVID-19 it seems prudent to withhold any systemic chemotherapy, unless entirely non-immunosuppressive, and to challenge the need for steroids until patients have fully recovered from COVID-19. More complicated is the situation of brain tumor patients tested for COVID-19 as part of a screen, who come back positive, but are asymptomatic for COVID-19. Here, a careful evaluation of risk and benefit is necessary and moderate delays of systemic chemotherapy may be a preferred option.

Conflicts of interest

MW has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, OGD2, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb, Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen.

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Key considerations for clinical practice

General
Prioritize transparent communication on risks and benefits of all interventions and prioritize advance care planning.
Challenge the urgency for repeat scanning and outpatient visits in patients in stable conditions who are asymptomatic, notably those with less aggressive tumors.
Avoid the use of treatments, such as reirradiation combined with steroids or potentially toxic systemic chemotherapy, for situations where there is no evidence for clinically relevant benefit.
Be absolutely rigorous in controlling the need for steroid prescriptions (“as little as possible, as much as needed”).
Carefully and individually weigh risks and benefits of continued participation for brain tumor patients already enrolled onto clinical trials, with consideration of national and institutional regulations.
Advise patients and caregivers to strictly adhere to local measures of limiting the spread of COVID-19.
Specific
Consider postponing resection or biopsy of non-contrast enhancing primary brain tumors with stable neurological symptoms
Consider hypofractionated radiotherapy in situations where this probably does not compromise outcome, e.g., in patients with brain metastases or with MGMT promoter-unmethylated glioblastoma.

Weigh benefit versus risk of alkylating agent chemotherapy in patients with gliomas lacking MGMT promoter methylation, notably patients with recurrent disease, reduced performance status, or in advanced age.
Consider conservative rather than courageous dosing of chemotherapy notably in situations where there is no urgent treatment need and where prolonged treatment is likely to provide benefit, e.g., in patients with lower WHO grade oligodendroglioma and astrocytoma